

QUANTUM DOTS IN DRUG TARGETING – A REVIEW

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ABSTRACT

Quantum dots are rapidly gaining interest for application in cancer cell imaging, and it has been shown that combining the drug delivery capabilities of polymers with cell imaging properties yields the best results. The pharmacokinetics research of QDs is the primary need for determining their safety. A typical QD's primary structure consists of a metalloid crystalline core that can be encased within a thin shell to protect the core and improve both electronic and optical characteristics. The hydrophilic I-III-VI type QDs that were created were also discovered to have the potential to be fluorescent probes for the identification of biomolecules and proteins. QDs were stable in vivo, did not agglomerate, and could identify all cell types in the embryo. QDs might be useful for detecting diseases and poisons, as well as identifying their features, such as pathogenicity. QDs' sensitivity and multiplexing capability for in vitro detection of several protein or nucleic acid tumor cell markers that alter at different stages of cancer, QDs have been utilized to regulate brain cells in a novel coupling of quantum physics and neurology.

Keywords: *Quantum Dots, Core Type, Core Shell Type, Alloyed Quantum Dots, Synthesis of Quantum Dot, Applications of Quantum Dots.*

INTRODUCTION

Nanotechnology, as a growing subject, has the potential to revolutionize health as well as many other fields such as textiles, electronics, and energy generation. Because of the material composition, nanotechnology, the utilization of nano-sized molecules, offers unique qualities such as self-assembly, stability, biocompatibility, specificity, and drug encapsulation. Because of their distinct properties, quantum dots (QDs), also known as semiconductor nanocrystals, are the chosen nano-carrier for chemotherapeutics^[1].

A quantum dot is a bit of matter in which the excitations are contained in all three spatial dimensions. As a result, the electrical characteristics of such materials are midway between those of bulk semiconductors and those of discrete molecules. It is first found by Alexei Ekimov in 1980s. Mark Reed created the phrase "quantum dot."^[2]

QUANTUM DOTS SEMICONDUCTOR

Quantum dots are semiconductors with electronic properties that are highly dependent on the size and form of the individual crystal. The smaller the crystal, the broader the band gap, the greater the difference in energy between the highest valence band and the lowest conduction band becomes, requiring more energy to excite the dot and releasing more energy when the crystal returns to its resting state. Because of their unique optical properties, such as broad absorption with narrow photoluminescence spectra, high quantum yield, low photo bleaching, and resistance to chemical degradation, semiconductor nanocrystals known as quantum dots (QDs) have been increasingly used as biological imaging and labelling probes.^[2] QDs, which were first conducted to determine surface kinetics, are now successfully used as both drug delivery agents and diagnostic markers.

It is made up of a semiconductor core material, which is responsible for fundamental optical features including light absorption and emission. The core material is further encased within another semiconductor material with a bigger spectral band gap, which improves the optical characteristics of the QDs and reduces chemical assault. The remarkable optical features of these colloidal semiconductor NCs are due to a limited 3D quantum regimen.^[3]

CLASSIFICATION OF QUANTUM DOTS

Qds are made up of elements of group II – VI, III – V, IV in periodic table. This is the chemical composition.

It is also classified into

- a) Core-type
- b) Core-shell
- c) Alloyed quantum dots ^[4]

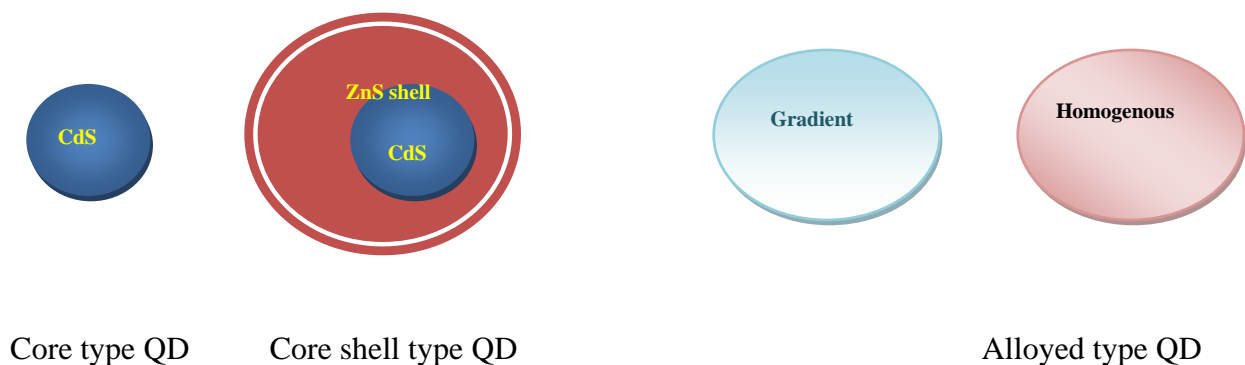


Figure 1: Classification of Quantum

A) CORE-TYPE

CdX (X=Se, S, or Te) QDs are the most studied QDs. The released cadmium ions, on the other hand, are to blame for the reported cytotoxicity of cadmium-based QDs, which limits their future practical usage. However, with the growing need for more biocompatible QDs as signal reporters, heavy metal-free QDs such as group IV QDs, which include carbon-based QDs and silicon or germanium QDs, have been produced.^[4]

B) CORE-SHELL

Core-shell QDs are 2nd generation products that are commonly utilized to modify the photo-physical characteristics of basic QDs. Their shell is specially constructed to increase the photo-stability and photoluminescence efficiency of basic QDs by several orders of magnitude. The core and shell are

commonly made of semiconductors of type II-VI, IV-VI, and III-V with configurations such as (CdS) ZnS, (CdSe) ZnS, (CdSe) CdS, and (InAs) CdSe.^[4]

It is further classified into three types

- i) Type I
- ii) Type II
- iii) Quasi type II

Type I

Type I core/shell QDs display band alignment, in which the band-gap of the core material is smaller than that of the shell, restricting both electrons and holes into the core area and resulting in higher photoluminescence quantum yield (PLQY) and photo-/chemical-stability, which is advantageous to luminescent QD-devices such as luminescent solar concentrators (LSCs) and light-emitting diodes (LEDs)^[5]

Type II

The staggered CB and VB edges of core and shell materials in Type-II core/shell QDs result in spatial separation of electrons and holes in distinct locations of core/shell QDs.^[5]

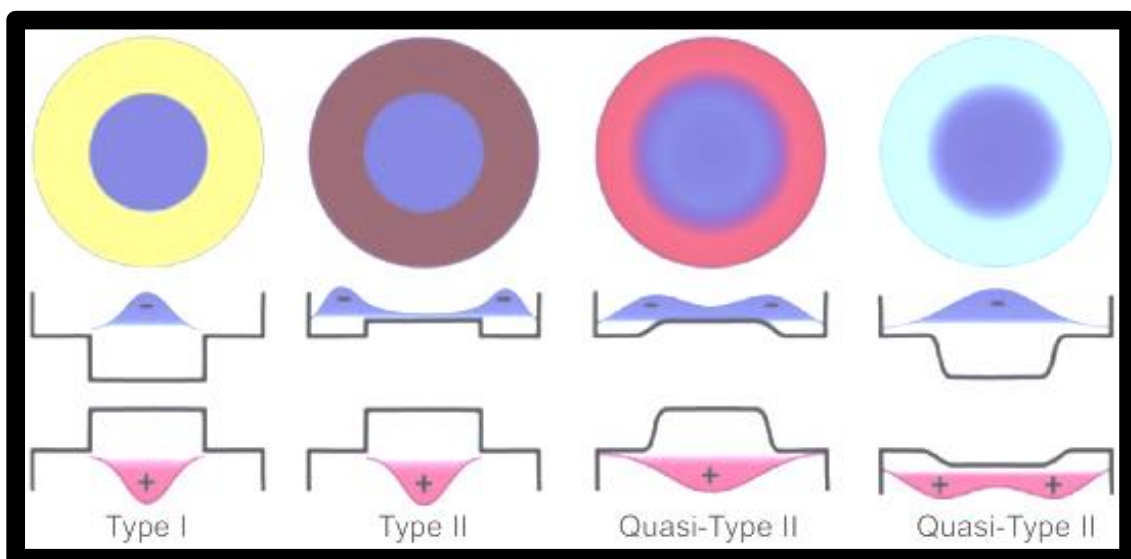


Figure 2: Classification of Core Shell

Quasi Type II

Low CB and VB offsets in quasi-type II core/shell QDs allow one kind of charge transfer to be delocalized into the shell region while the other type of charge carrier remains contained in the core region.^[5]

C) ALLOYED QUANTUM DOTS

Alloying QDs are a popular topic in QD research. Alloyed QDs having both homogeneous and gradient internal structures, such as cadmium selenium sulphide (CdSeS), are the most recent generation of extremely luminous QDs.^[4]

It has four types that is traditional core-shell CdTe-CdSe dots, reversed core-shell dot, homogenous and gradient alloyed dots.^[6] In homogeneous QDs, the internal structure is uniform, so the composition is the same everywhere on a single QD, whereas in gradient QDs, alloy compositions vary radially, which means that the ratio of the first and second semiconductors changes gradually from the core to the surface in a gradient internal structure. The internal structure of alloyed QDs is a key factor in their applications since gradient and homogeneous alloyed QDs have distinct optical and electrical properties.^[4]

SYNTHESIS OF CORE TYPE CADMIUM SULFIDE QUANTUM DOTS

Tsuzuki T et al., has said that Anhydrous CdCl₂ powder, Na pieces, S powder, and NaCl powder were employed as starting materials in this work. Preliminary to use, the CdCl₂ and NaCl powders were vacuum dried to utilize. The reactants were placed in a hardened steel vial and sealed with steel balls in an Ar-gas environment of high purity Milling was carried out using a Spex 8000 mixer/mill with a ball-to-powder mass ratio ball diameters ranging. The NaCl was removed after grinding by washing the powder as-milled 5 times in demonized and deoxygenated water. Then vacuum dried at ambient temperature. The initial Na₂S powder was made by milling stoichiometric quantities of Na and S with NaCl as a diluent to avoid combustion and allow for the formation of highly separated Na₂S particles. NaCl to Na₂S volume ratio. It was discovered that milling for 1 hour with grinding balls produced Na₂S with a crystallite size. To create CdS, a quantity of CdCl₂ was added to a mechanically alloyed combination of Na₂S and NaCl. The NaCl diluent was left in the initial powder to aid in the production of distinct CdS nanoparticles in the NaCl matrix during grinding process.^[7]

SYNTHESIS OF CORE-SHELL INDIUM PHOSPHIDE/ ZINC SULPHIDE QUANTUM DOT

Brunetti V et al., he done the synthesis of InP/ZnS in a flask fitted with a thermometer and a condenser, hexadecyl amine, stearic acid, zinc undecylenate, and indium chloride were combined with octadecene (ODE) under an inert atmosphere (Ar or N₂). The reaction mixture was quickly heated before adding tris-(trimethylsilyl) phosphine. The solution was then chilled in a water bath. At room temperature, zinc diethyldithiocarbamate was added to the mixture, and the temperature was raised. When the thermometer reached the desired temperature, the scheduling started. After cooling the reaction mixture to room temperature, toluene was poured. After centrifuging the mixture at for 5 minutes, the precipitate was discarded. By adding ethanol to the orange supernatant solution, the particles were precipitated and collected by centrifugation. In 3 ml of toluene, the InP/ZnS particle was redissolved. By adding butanol borate buffer, and mercaptopropionic acid of a QD solution, QDs were transported into an aqueous environment. For 15 minutes, the mixture was heated. After separating the two phases, the aqueous layer containing the InP/Zn-MPA was purified by four rounds of washing/filtration using a 10 kDa molecular weight cut-off filter with 50 mM borate buffer at pH 9. Purified QDs were dissolved in borate buffer at the required pH and kept at 4 °C.^[8]

SYNTHESIS OF CORE-SHELL CADMIUM SELENIDE / ZINC SULPHIDE QUANTAM DOT

Brunetti V et al., has said that ODE, cadmium oxide (CdO) and oleic acid were added. This mixture was degassed for 5 minutes before being heated under nitrogen to 250°C till it turned colourless. TOPSe was made by combining Se, trioctylphosphine and ODE in a sealed container under N₂ until the solution became bright yellow. At 260°C, this solution was immediately injected into the CdO-ODE combination. Following the injection of the selenium precursor, the solution was cooled using a water bath. TOP, hexamethyldisilathiane, and dimethylzinc were diluted with ODE under a N₂ environment. A total of this solution was injected into the CdSe QD solution at 170°C, then add the remaining drop by drop over 5 minutes. The temperature was then let to fall and then kept at 100 C for 3 hours for QD annealing. QDs were purified using three separate extractions of 1: 1 hexane-methanol in a separatory funnel. Unreacted CdO and oleic acid are soluble in the lower methanol

phase and may be discarded, but QDs are only soluble in the higher hexane-ODE phase. To precipitate the QDs, a substantial excess of ethanol was added to the hexane phase, and the sample was centrifuged for 1 minute. The QD pellet was immersed in a sufficient amount of toluene to achieve an optical density of roughly 4 at 400 nm. Aliquots of this QD solution were kept in airtight containers in the dark. Using ligand exchange, QDs were transported into an aqueous environment. 1 ml of concentrated QD solution was diluted to with methanol for this purpose. MPA was added to the mixture, and the pH was adjusted to 10 using tetramethyl ammonium hydroxide pentahydrate (TMAH). For 12 hours, this solution was stirred at room temperature. Lastly, QDs were isolated from excess MPA by precipitation after the addition of excess ethyl acetate, followed by 5 minutes of centrifugation. The supernatant was removed, and the pellet was air dried for 1 hour at room temperature. Finally, the pellet was re-dissolved in 2 ml of doubly distilled water, and the solution was filtered through a 0.2 μ m membrane filter before being kept at room temperature and light-protected.^[8]

SYNTHESIS OF CdTeS ALLOYED QUANTUM DOT

Mao W et al., said that sodium borohydride was dissolved in distilled water after being degassed in ice-water baths for 0.5 h under nitrogen flow. Tellurium powder was promptly added, and after 0.5 h of reaction in the ice-water baths under nitrogen flow, the bottle was sealed and placed in a refrigerator (4 C) for continued reaction for more than 8 hours. Slowly dissolving the black tellurium powder produced a clear purple sodium hydrogen telluride (NaHTe) solution. Then, distilled water, CdCl₂ was dissolved, and 3-mercaptopropionic acid (MPA) was added. The pH was adjusted to 9.0 by adding 2 mol NaOH solution dropwise. The oxygen-free NaHTe solution was then quickly introduced into the aforesaid solution while vigorously swirling. Finally, the mixed precursor solution was transferred to a Teflon-lined stainless-steel autoclave and kept at 180 C for a set period of time before being cooled to ambient temperature using a hydro-cooling technique. Following the initial heating, a succession of CdTeS alloyed QDs of varying sizes were formed at regular time intervals.^[9]

DRUG DELIVERY OF QUANTUM DOT

Drug delivery has been one of the most exciting uses of nanotechnology in treating illnesses like cancer. CdTe QDs are the core group of materials utilized in drug delivery. In certain study, QDs have been employed for delivery of pharmaceuticals. Quantum dots might potentially be employed in gene targeting genes of cells like cancerous cells. The unique attributes of nano-particles which has given birth to the introduction and broad uses of nanotechnology is ascribed to its one-of-a-kind properties, notably substantial volume/surface ratio, capability of surface tailoring, and multi-functionality.

As super-semiconducting nanomaterials with exceptional fluorescence characteristics, CdTe QDs are highly promising candidates for usage in chemical sensors, optical switches, display systems, and bio-labels, owing to their optical qualities. Since Te_2^- is particularly sensitive to the presence of oxygen, thioglycolic acid (TGA) is utilised as a preservative for altering the surfaces of the CdTe QDs throughout the production method. The result is therefore historicized CdTe QDs negative surface charges.

CdTe QDs are also employed in numerous biological applications including imaging, labelling and diagnostics applications or photodynamic treatments, and targeted drug administration. cysteamine-modified CdTe QDs (Cys-CdTe QDs) in CSL research on bioimaging and target treatment and showed that positively charged Cys-CdTe QDs a synergetic effect, which promotes the in vitro targeted delivery of CSL to the drug-resistant cell line $\text{K}_{562}/\text{A}_{02}$ of human leukaemia cell K_{562} . Quantum dots are rapidly gaining interest for application in cancer cell imaging, and it has been shown that combining the drug delivery capabilities of polymers with cell imaging properties yields the best results.^[10]

QUANTUM DOTS INTERACTIONS WITH ORGANS

QDs are often introduced into the body by inhalation, ingestion, or intravenous injection as part of their medicinal uses or occupational condition. In recent years, substantial research has been conducted on the toxic impact of QDs and the mechanism of toxicity in vitro. However, in vivo research produces different results than in vitro studies because cells and QDs act differently in both

situations. Animal investigations were able to provide information on both the biological and chemical fates of QDs inside an intact biological system.

In vitro studies provide an excellent model for studying the possible harmful impacts of QDs. The pharmacokinetics research of QDs is the primary need for determining their safety. ADME is the most fundamental foundation in biosafety assessment. Only in vivo research provides ADME information, whereas in vitro studies do not. The usefulness of ADME studies in the biosafety evaluation of QDs has long been recognised and promoted. Thus, it is critical to corroborate in vitro findings with in vivo research. QD-705 (QD with a CdTeSe core, ZnS shell, and PEG - 5000 coating) underwent detailed physiology-based pharmacokinetic (PBPK) experiments. They discovered that QD-705 has a plasma half-life of 18.5 hours and that the liver, kidney, and spleen are the primary organs of QD accumulation.

The research revealed that liver and spleen are the early accumulation organs, and after extended time exposure, QDs are identified in kidney. Only in the kidney does QD buildup rise with time. The elimination of hydroxyl-silica coated QDs via the stools and urine. The liver and kidney are shown to be the primary organs of QD accumulation.^[11]

PHYSICOCHEMICAL PROPERTIES OF QUANTAM DOTS

A typical QD's primary structure consists of a metalloid crystalline core (e.g., CdS, CdSe, or CdTe) that can be encased within a thin shell (e.g., ZnS) to protect the core and improve both electronic and optical characteristics. The core is made up of a variety of metal complexes, including magnetic transition metals, noble metals, and semiconductors (for example, PbS, GaAs, Ag₂Se, ZnTe, InP, and Si). During the synthesis process, a thin shell forms on the surface of the metalloid crystalline core. QDs' physicochemical qualities are determined by particle size and shape, core and shell composition, and surface chemistry.

QDs may be easily produced in either an organic solvent or an aqueous solution, allowing for more processing flexibility. Nonetheless, the surface characteristics of QDs in organic solvent differ dramatically from those in aqueous solution. Organic QDs have hydrophobic ligands, which make them soluble in the organic phase. Meanwhile, the surface of organic QDs may be changed with

hydrophilic ligands to make them water-soluble and biocompatible, but aqueous QDs are water-soluble by nature and do not require surface modification. Surface modification of QDs may be accomplished using a variety of approaches.

QD surfaces, for example, can be coupled with amphipathic molecules like polyether or octadecylamine polymers, coated with bifunctional molecules like mercaptoacetic acid, and enclosed within micelles. Furthermore, the surface of QDs can be further modified with target ligands such as oligonucleotides, polypeptides, or antibodies to route QDs to particular places within cells or organs in the body. Many QD designs are anticipated to exhibit a one-of-a-kind combination of physicochemical features, allowing QDs to interact with biological entities.

The optical characteristics of QDs are heavily influenced by particle size and chemical composition. QDs have great photostability, strong fluorescence emission intensity, a broad excitation spectrum, and a limited emission spectrum when compared to organic fluorophores. QDs' broad excitation and narrow emission spectra make them ideal for many bioimaging applications, and different colours are employed to encode peptides, proteins, and tiny molecules. QDs are stimulated by absorbing external energy, which causes electrons to move from the ground state to the excited state. When the QD system returns to its ground state, the absorption is followed by the release of energy and the partial generation of photons. Furthermore, because of their high signal intensity and long emission lifetime, QDs outperform typical organic fluorophores as very appealing fluorescent probes for long-term intracellular detection.^[12]

APPLICATIONS OF QUANTUM DOTS

BIO-SENSORS

The hydrophilic I-III-VI type QDs that were created were also discovered to have the potential to be fluorescent probes for the identification of biomolecules and proteins. By transferring oleylamine-capped AgInS₂/ZnS QDs to a water phase and replacing the capping ligand with MPA, the functionalized QDs could detect glucose in conjunction with redox enzymes. Based on the fluorescence quenching of the Fib-CuInS₂ QDs complex by thrombin, MPA-capped CuInS₂ QDs directly generated by a hydrothermal technique were used as a fluorescence probe for the detection of thrombin. They then described the 3-aminophenyl boronic acid-functionalized CuInS₂ QDs as a

near-infrared fluorescence probe for dopamine assessment based on the interaction of neighbouring dopamine diols with phenylboronic acid. Based on the interaction between amino groups on the surface of CuInS₂ QDs and sulphate groups in heparin, L-cysteine capped CuInS₂ QDs might be used as a nano sensor for determining heparin and heparinise.^[13]

CELL TRACKING

QDs contained in phospholipid micelles were utilized to mark individual blastomeres in xenopus embryos. These encapsulated QDs were stable in vivo, did not agglomerate, and could identify all cell types in the embryo. The QD-micelles were not hazardous to the cells at the levels necessary for fluorescence visualization ($2 * 10^9$ /cell), but doses of ($5 * 10^9$ /cell) did cause abnormalities. The QDs were restricted to the injected cell and its descendants, albeit unintentional translocation to the nucleus was seen at a certain stage of embryo development. Another group that labelled Dictyostelium discoideum discovered that cell labelling may last for more than a week and that QD labelling had no discernible effects on cell shape or function.

Differently coloured QDs might potentially be employed to mark distinct populations in order to evaluate the effect of hunger on D. discoideum development. These cells could be followed for extended periods of time with no noticeable fluorescence degradation. Most zebrafish embryo blastomeres labelled with QDs and co-injected with CFP, a commonly used lineage marker, exhibited QD passage to daughter cells, however some cells expressing CFP fluorescence did not show QD fluorescence. This was hypothesized to be due to QD aggregation, resulting in uneven inheritance by daughter cells. This is a well-known issue, along with fluorescence loss and instability in the QD structure in biological fluids.^[14]

DETECTION OF PATHOGENS

QDs might be useful for detecting diseases and poisons, as well as identifying their features, such as pathogenicity. A number of studies have had positive results, and the ability to employ multiplexed imaging is very valuable in this field. So far, several pathogens have been targeted, including Cryptosporidium parvum and Giardia lamblia, E. coli 0157:H7, Salmonella Typhi, and L. monocytogenes. When compared to two regularly used commercial staining kits, simultaneous multiplexed labelling of C. parvum and G. lamblia utilising immunofluorescent staining techniques

with QD fluorophores provided an excellent signal-to-noise ratio of 17, with greater photostability and brightness. One research, however, discovered that the QD-based test was not as sensitive as ELISA-based approaches.^[14]

ANTI CANCER APPLICATION

One of the most difficult aspects of cancer treatment is determining the status of a tumor and its potential for therapeutic treatment. Near infrared QDs have strong tissue penetration and a low background, making them suitable for analysing lymph node metastases. It has been shown that QDs injected into two model cancers rapidly migrate to sentinel lymph nodes. In one investigation, scientists discovered that four rhesus monkeys given cadmium-selenide QDs stayed healthy for more than 90 days. Blood and biochemical indicators remained within normal levels, and no anomalies were seen in the major organs. The animals did not slim down. QDs' sensitivity and multiplexing capability for in vitro detection of several protein or nucleic acid tumour cell markers that alter at different stages of cancer.

QDs identify and label tumor cells using one of two approaches. In active targeting, QDs can attach to tumor cells by being next to tumor-specific active binding sites. As a result, immune fluorescent probes containing antibodies are developed to detect these malignancies. A QD system can detect the presence of RSV (Respiratory Syncytial Virus) particles in a couple of hours. It is also extremely sensitive, allowing the virus to be detected early in the disease's progression.^[15]

IN NEUROSCIENCE

In brain research, QDs are viewed as a novel tool with extraordinary potential. These nanomaterials are suitable for research that are hampered by the limited architecture of neuronal and glial interactions, such as the tiny size of the synaptic cleft or the connection between an astrocyte and a neuron. For the first time, QDs have been utilized to regulate brain cells in a novel coupling of quantum physics and neurology. Controlling the brain may one day enable a non-invasive therapy for conditions such as depression, Alzheimer's, and epilepsy. QDs may be utilised to cure blindness in the near future by stimulating damaged retinal cells.^[15]

CONCLUSION

Quantum dot is one the most advanced tool for specific target site drug delivery. It can selectively target on tumor biomarkers and tumor vasculatures. It can be used in gene delivery which is less in cost and toxicity. It has also less cytotoxicity. It has a wide future in cellular process, intracellular delivery. This toxicity can be reduced by changing the core in non-metallic material. Fluorescent probes from quantum dots can helpful in applying biorecognition of antibodies, peptides, nucleic acids etc. These Quantum dots can be also further applied in gene therapy, fluorescent labeling of cellular protein, In vivo animal imaging, tumor biology investigation. Nanotechnology with quantum dot has great future. It will definitely redesign the future medicine technology.

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